Rational Pharmaceutical Management Plus
Technical Visit to Brazil: Trip Report
December 3-December 14, 2004

Thomas Moore

December 17, 2004

Rational Pharmaceutical Management Plus
Center for Pharmaceutical Management
Management Sciences for Health
4301 N. Fairfax Drive, Suite 400
Arlington, VA 22203
Phone: 703-524-6575
Fax: 703-524-7898
E-mail: rpmplus@msh.org

This report was made possible through support provided by the U.S. Agency for International Development, under the terms of cooperative agreement number HRN-A-00-00-00016-00. The opinions expressed herein are those of the author(s) and do not necessarily reflect the views of the U.S. Agency for International Development.

About RPM Plus

The Rational Pharmaceutical Management Plus (RPM Plus) Program, funded by the U.S. Agency for International Development (cooperative agreement HRN-A-00-00-00016-00), works in more than 20 developing countries to provide technical assistance to strengthen drug and health commodity management systems. The program offers technical guidance and assists in strategy development and program implementation both in improving the availability of health commodities—pharmaceuticals, vaccines, supplies, and basic medical equipment—of assured quality for maternal and child health, HIV/AIDS, infectious diseases, and family planning and in promoting the appropriate use of health commodities in the public and private sectors.

Abstract

Rational Pharmaceutical Plus is providing technical assistance to the *Professor Hélio Fraga TB Reference Center* in the area of TB control. RPM Plus visited Brazil from December 3-December 14 to conduct a stakeholders meeting for transition of national TB drug treatment regimens to use of fixed dose combination (FDC) products. The stakeholders included persons from national quality assurance institutes, research facilities, pharmaceutical producers, regulatory agencies and the national TB program. A regimen for a three FDC product was approved and a timeline for implementation was established. The stakeholders meeting was well received and will be used as a model for future collaboration among government agencies.

Recommended Citation

Moore, Thomas. 2004. *Technical Visit to Brazil: Trip Report December 03-December 14, 2004.* Submitted to the U.S. Agency for International Development by the Rational Pharmaceutical Management Plus Program. Arlington, VA: Management Sciences for Health.

Key Words

tuberculosis, MDR-TB, TB drug quality, FDC, stability study, bioavailability

Contents

Acronyms

ANVISA	National drug regulatory agency in Brazil
DMIS	Drug Management Information System
DOTS	directly observed therapy short-course [WHO TB Control Strategy]
FIOCRUZ	Brazilian National Research Institute
FDC	Fixed dose combination products
INCQS	National Institute of Quality in Health in Brazil
LACENS	State laboratory system in Brazil
MDR-TB	Multi-drug resistant tuberculosis
MOH	Ministry of Health
SVS	National health administration system in Brazil
TB Center	TB Reference Center Professor Helio Fraga (National TB Control)
USAID	United States Agency for International Development
VISAs	State health regulatory agency in Brazil

Background

Brazil is ranked 14th of 22 countries having the highest burden of tuberculosis (TB) in the world, and has approximately 110,000 new cases annually and 1,300 patients being treated for multi-drug resistant TB (MDR-TB). Approximately 3,000 persons die annually in Brazil from the disease.

In November 2003, USAID funded the Rational Pharmaceutical Management Plus (RPM Plus) program to support the TB fighting effort by providing technical assistance in the area of Tuberculosis pharmaceutical management. RPM Plus is working with its counterparts at the *TB Reference Center Professor Hélio Fraga* (TB Center) and National Institute of Quality in Health (INCQS) in carrying out the activities. The TB Center is responsible for developing, analyzing and transferring technologies to combat TB in the country and monitoring the approximately 1,300 cases of multi-drug resistant TB (MDR-TB). INCQS provides quality testing of pharmaceutical products and lab services through its technical assistance and oversight of the state laboratories (LACENS).

Thomas Moore, manager of project activities for RPM Plus in Brazil, traveled to Brazil in order to participate in the first stakeholders meeting discussing acceptance and development of 3 and 4-drug fixed dose combination (FDC) TB medicines with the aim of supporting the DOTS strategy in-country. This activity is one of the main objectives of the RPM Plus work plan for FY04. Mr. Moore also planned to meet with TB Center, INCQS partners and RPM Plus staff to discuss on-going RPM Plus activities.

Scope of Work

The scope of work was as follows:

1. Participate in a stakeholder meeting to develop strategy and plan for introducing FDCs in the Brazil national TB program.

2. Work with partners at the national TB Center

3. Work with RPM Plus local staff to:
   - Finalize deliverables of RPM Plus activities already completed
   - Identify the immediate next steps of work
   - Outline next steps for 2005

4. Brief/debrief USAID officials in person or electronically as requested

Activities

1. **Participate in a stakeholders meeting to develop strategy and plan for introducing FDCs in the Brazil national TB program**.

The stakeholders' workshop took place in Rio de Janeiro at the Farmanguinhos government manufacturing facility December 6-7, 2004. Approximately 30 people were in attendance, including personnel from the MOH (the National TB Control Program, the Pharmacy Department and the Department of Pharmaceutical Technology), ANVISA (national regulatory authority), FIOCRUZ (national research institute), INCQS (national quality assurance institute), Farmanguinhos (government pharmaceutical manufacturing company), TB Network (Rede-TB), Reference Center Profesor Helio Fraga (TB Center) and RPM Plus. See Portuguese version of the workshop program in Annex 1.

Joel Keravec, RPM Plus local technical coordinator, organized and facilitated the workshop. Objectives included the following:

- Define work activities based on workshop presentations
- Focus only on essential areas to be discussed
- Define specific objectives to implement a national strategy with responsibilities of each stakeholder and the resources needed
- Elaborate a Plan of Action and timeline, defining the next steps

Thomas Moore presented latest data on global FDC use including product formulations, location of manufacturing sites, procurement prices, countries that use FDCs, World Health Organization recommendations and abstracts from studies demonstrating potential problems with rifampicin bioavailability, especially in poorly designed FDC products.

Other presentations were made as follows:

- Dr. Joseney Santos, National TB program Director on current treatment regimens and support for switching to FDCs to improve patient and health worker adherence to national guidelines and improvement in treatment outcomes
- Dr. Margareth Dalcolmo, Coordinator of national MDR-TB treatment program on national consensus for treating TB which includes the three-drug FDC for new cases
- Dr. Nubia Boechat, Diretor of Farmanguinhos on current TB products produced for the government of Brazil and other TB products under stability studies
- Kelton Berreto, staff of national ANVISA on regulatory viewpoint of a new FDC product for TB
- Dr. Andre Daher, pharmacologist of FIOCRUZ on what should be the recommended doses of a FDC in Brazil
- Dr. José Rodrigues, Director of Nanocore, member of Rede-TB on perspective of FDC development by the Rede-TB

Discussions ensued about the current TB products used in Brazil and the need to include other kinds of products as well as the FDC. In essence, the decision was unanimously made to design and implement the following TB products:

- Isoniazid 300 mg tablet for adult prophylaxis
- Children's syrups of Isoniazid and Rifampicin
- Change the two-drug rifampcin-isoniazid capsule to a compressed tablet formulation
- Three drug FDC containing rifampicin 300 mg, isoniazid 200 mg and pyrazinamide 250 mg
- Three-drug FDC containing 150 mg, isoniazid 100 mg and pyrazinamide 500 mg

Because of known bioavailability problems in poor quality production processes both stability and bioavailability studies will be conducted on the above formulations once test batches have been manufactured by Farmanguinhos.

The work will be staggered and the different product formulations will become available at different times over the next 30 months, the estimated time taken to bring the most complicated products, the three-drug FDCs, to fruition.

The stakeholders decided that a second meeting would be held in March 2005 to discuss progress on the product formulation agenda. RPM Plus will again facilitate this workshop.

The national treatment regimen for new cases is slightly different from that recommended by the WHO; this point came into discussion frequently. The stakeholders agreed that the current drug strengths were appropriate for the Brazil population as they have been in use for 25 years.

A four-drug FDC was discussed for re-treatment cases (about 10,000 cases in Brazil), but the group preferred to discuss this topic at a later time.

2. Work with partners at the national TB Center and INCQS

RPM Plus met with Drs. Miguel Aiub Hijjar and Maria-José Procópio, Director and Vice-Director of the TB Center, and later with Dr. Andre Gemal of INCQS. Discussions focused on accomplishments for the year 2004, planned activities for 2005 and continuing activities for 2006.

The RPM Plus activity for studying the treatment regimen that would replace ethionamide with levofloxacin was the center of attention at the TB Center discussions, as the study protocol was programmed to be finished by end of 2004; it is still not in final draft form. However, the committee set up to develop the protocol expects to have the study protocol finalized by end of January 2005. RPM Plus will provide the study monitor for this activity.

Overall Drs. Hijjar, Procopio and Gemal are pleased with the RPM Plus management and technical skills in carrying out the four streams of activity on the RPM Plus work plan.

3. Work with RPM Plus local staff

Thomas Moore met with Joel Keravec (Technical Coordinator), Ana Paula Vervloet (Operations Manager) and Jocilaine Leite (administrative assistant) to discuss RPM Plus activities. The team collected the 2004 deliverables of RPM Plus activities already completed and, based on discussions with partners at the TB Center and INCQS, prepared a spreadsheet of continuing and future-related activities, as requested by the parnters.

Accomplishments and requests for future RPM Plus technical assistance can be viewed on the attached power point handouts (Annex 3 and 4).

4. Brief/debrief USAID officials

Joel Keravec and Thomas Moore met with Patricia Paine, TB focal point and Mike Burkley Health Team Leader at the USAID mission in Brasilia. RPM Plus debriefed USAID on the outcome of the FDC stakeholders meeting and presented a power point presentation of accomplishments for 2004, planned activities for 2005 and partner requests for continuing RPM Plus assistance for 2006. A copy of the briefing document (Annex 2) and power point presentation (Annexes 3 and 4) are attached to this report.

Collaborators and Partners

Dr. Miguel Aiub Hijjar, Director, TB Center
Dra. Maria Jose Procópio R de Oliveira, Deputy Director, TB Center
Dr. Andre Gemal, Director of INCQS (National Institute of Quality in Health)
Dr. Joseney Santos, National TB program Director
Dr. Margareth Dalcolmo, Coordinator of national MDR-TB treatment program
Dr. Nubia Boechat, Diretor of Farmanguinhos
Kelton Berreto, staff of national ANVISA
Dr. Andre Daher, pharmacologist of FIOCRUZ
Dr. José Rodrigues, Director of Nanocore member of Rede-TB
Patricia Paine, USAID/Brazil
Mike Burkly, USAID/Brazil

Next Steps

- RPM Plus consultants and the committee for changing the ethionamide TB regimen will finalize the study protocol in January 2005
- RPM Plus will organize a stakeholders workshop to discuss FDC progress in March 2005
- RPM Plus/Brazil will present the MOST for labs tool to RPM Plus staff in Arlington—tool was adapted for certifying quality control laboratories for testing TB products
- RPM Plus will continue to work with the TB Center in decentralizing MDR-TB management information system to the states
- RPM Plus will continue to work with INCQS to decentralize lab certification to the state reference laboratories (LACENS)

Annex 1

FDC Stakeholders Workshop

OFICINA DE TRABALHO SOBRE
INTRODUÇÃO DE ASSOCIAÇÃO FIXA DE FÁRMACOS /
COMBINAÇÃO EM DOSE FIXA
PARA TUBERCULOSE

PROGRAMA

Data: ***06/12/2004 e 07/12/2004***
Local: ***Farmanguinhos - Nova Sede / Jacararepaguá***
Horário:dia 6/12/2004 ***14h00 – 17h15*** *dia 7/12/2004* ***09h00 – 17h15***

Participantes:

Dr Joseney dos Santos, Coordenador do Programa Nacional de TB
Dr.ª Marília Cunha - Diretora da Assistência Farmacêutica - MS
Dra Nubia, Diretora de Farmanguinhos - Fiocruz
Dr. André Gemal - Diretor do INCQS
Dr Miguel Hijjar, Diretor do CRPHF/SVS
Dr Sergio Nishioka, Gerente do GEPEC/Anvisa ou Dr Kelton Barreto GEPEC/Anvisa
Dr.ª Keila Marzochi - Diretora do IPEC
Dra MJ Procopio, CRPHF/SVS
Dra Margarete Dalcolmo, CRPHF/SVS
Dr Celio Lopes Silva - Coordenador da Rede TB
Dr Afranio Kritski - Rede TB
Dr José Maciel Rodrigues Júnior - Rede TB
Dr Reynaldo Dietze - Rede TB
Dra Zenaide, Assistência Farmacêutica
Dr Tom Moore, MSH, Management Sciences for Health, USA
Dr Joel Keravec, Projeto MSH, Brasil
Alessandra Viçosa - Departamento de Tecnologia Farmacêutica - Far
Grace Mafra - Departamento de Tecnologia Farmacêutica - Far
Dr André Daher - Assessoria de Planejamento e Gestão Tecnológica - Far
Sérgio Ruiz - Assessoria de Negócios - Far
Jorge Mendonça - Assessoria Executiva - Far
Dr. Marcus Souza - Departamento de Síntese Orgânica - Far
Solange Wardell - Departamento de Síntese Orgânica - Far
Dr. Ivan Neves Jr. - IPEC
Dr.ª Maria Cristina S. Lourenço - IPEC

Contexto geral

O tema da introdução terapêutica de Medicamentos contra Tuberculose com apresentação de dose fixa combinada de fármacos (3 em 1 ou/e 4 em 1) aparece de maneira recorrente em varias pautas de discussões, tanto nos congressos de associações profissionais como a Sociedade Brasileira de Pneumologia e Tisiologia, na Secretaria de Vigilância em Saúde do Ministério da Saúde (MS), área de Pneumologia Sanitária, na Secretaria de Ciência e Tecnologia e Insumos Estratégicos/MS, nas unidades da Fundação Oswaldo Cruz, na agenda de ações iniciadas pela rede TB, ou como solicitação da sociedade civil.

Uma das estratégias definida pelo Programa Nacional de TB/SVS em 2004 para combater a tuberculose é a introdução de associação de tuberculostaticos em uma única formulação (FDC: Fixed Dose Combination). E considerada uma estratégia valiosa para aumentar a taxa de adesão ao
tratamento do paciente e o sucesso da terapia, facilitar a prescrição e a logística de gerenciamento farmacêutico e diminuir riscos de resistência.

Varias iniciativas a diversos níveis e por diferentes instituições foram tomadas no sentido de introduzir Medicamentos contra Tuberculose com apresentação de dose fixa combinada de fármacos. Farmanguinhos desenvolveu uma formulação atualmente em fase de teste de estabilidade acelerada, a rede TB também desenvolveu uma formulação, a Anvisa publicou recentemente uma nova RDC sobre dose fixa combinada de fármacos...
Uma oficina de trabalho reunindo todos os atores envolvidos nesses processos era necessária, no intuito de discutir os pontos críticos a serem levantados, definir uma estratégia de abordagem comum, otimizar as ações e fortalecer as relações interinstitucionais. Esta oficina e organizada e coordenada por Projeto MSH junto com Farmanguinhos e será realizada nos dias 6 e 7 de dezembro de 2004 em Farmanguinhos – Sede de Jacarepaguá no Rio de Janeiro.

Explorar os mecanismos para introduzir este projeto para faz parte de um convênio firmado entre o Ministério da Saúde (MS), com o Centro de Referência Prof. Hélio Fraga (CRPHF), órgão do referência do Sistema Único de Saúde (SUS) para tuberculose, e a associação civil brasileira sem fins econômicos “Projeto MSH”, através do Programa Gestão Racional de Medicamentos (RPM Plus).

Este acordo vem ao encontro de diretrizes nacionais do MS de controle da tuberculose e outras pneumopatias, que prevê aumento de participação e celebração de parcerias entre órgãos governamentais e a sociedade civil, de forma complementar, buscando-se uma otimização dos insumos e aumento de capacidade de execução de projetos.

Objetivo Geral da oficina

- Definir uma estratégia interinstitucional para a introdução terapêutica de Medicamentos contra Tuberculose com apresentação de dose fixa combinada de fármacos (3 em 1 ou/e 4 em 1)

Objetivos específicos

- Estabelecer uma agenda de questões de natureza técnica com vistas à introdução da modalidade de tratamento da tuberculose na rede de serviços públicos, utilizando a apresentação de medicamentos em dose fixa combinada.

- Elaborar uma estratégia e um plano de trabalho com objetivos específicos e um cronograma para definir a organização e as modalidades de implementação deste projeto bem como as co-responsabilidades de cada ator**.**

- Articular acordos interinstitucionais para implementar uma agenda de trabalho com a chancela do Ministério da Saúde.

Organização da oficina:

A agenda foi dividida em 4 momentos:

1. Primeiro momento: definir o contexto de trabalho através de apresentações
2. Segundo momento: focar nos pontos essenciais a serem discutidos
3. Terceiro momento: definir objetivos específicos para implementação de uma estratégia nacional, com as responsabilidades de cada ator e as mobilizações necessárias.
4. Quarto momento: Elaborar um Plano de Ação com proposta de cronograma e definir os próximos passos

Annex 2

RPM Plus Program Activities Briefing Document
USAID Brazil Mission
December 13, 2004

- Stakeholders meeting on introduction of fixed dose combination (FDC) drugs for TB:
  - Took place on 6 and 7 December at Farmanguinhos new facility
  - Attended by 26 persons from National TB Program, MOH pharmacy department, Farmanguinhos, Army Manufacturing laboratory, Rede TB, ANVISA (Quality Surveillance), INCQS, Center Helio Fraga, FIOCRUZ Research Institute of Evandro Chagas, Projeto MSH
  - First time that industry, MOH programs, research institutions and national regulatory agencies have met to harmonize issues in product formulation, product demands, drug development, quality testing and registration. This model will now be used for other national programs such as malaria and HIV/AIDS
  - Discussion of any work previously done on FDC and its relevance to the recently approved National Consensus for treating TB (II Consenso Brasileiro de Tuberculose)
  - Consensus was made by all organizations and a plan for implementation of 3-drug FDC for esquema I, new cases, which represent about 85,000 cases annually
  - Outcome is huge in that it reduces the number of tablets from 5-9 depending on patient weight to 3-4 promoting health worker and patient adherence—should also affect the number of adverse reactions and patients abandoning treatment
  - Implementation timeline is 12-30 months due to bioavailability and stability studies of the new formulations for adults and children—different formulations will be phased in one at a time
  - Another important outcome of this activity is the replacement of capsules with tablet formulations like the rest of the world (capsules are less stable than compressed tablets when manufactured appropriately)

- Demonstration of Drug Management Information System for decentralizing diagnosis and treatment of MDR-TB at Center Helio Fraga
  - Design was completed in September including diagnostic and reporting procedures and data collection and reporting forms
  - Programming is almost complete

- Meeting with Centro Helio Fraga and INCQS-Fiocruz to discuss on-going activities in 2005 and needs for 2006

- Presentation to USAID mission of accomplishments and outputs in 2004, on-going activities in 2005 and needs for 2006

Thomas Moore—MSH Principal Program Associate for TB
Joel Keravec—Projeto MSH Technical Coordinator

Annex 3

RPM Plus Activities in Brazil

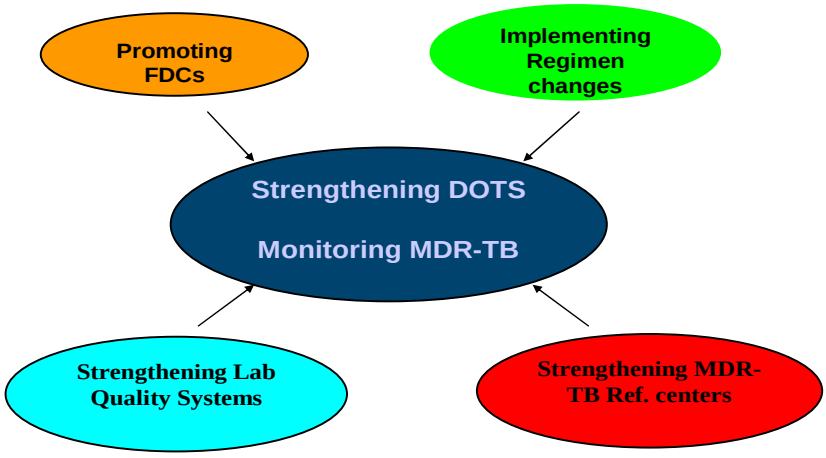
13 December 2004
USAID Mission

Thomas Moore
Joel Keravec

Projeto MSH

CRPHF

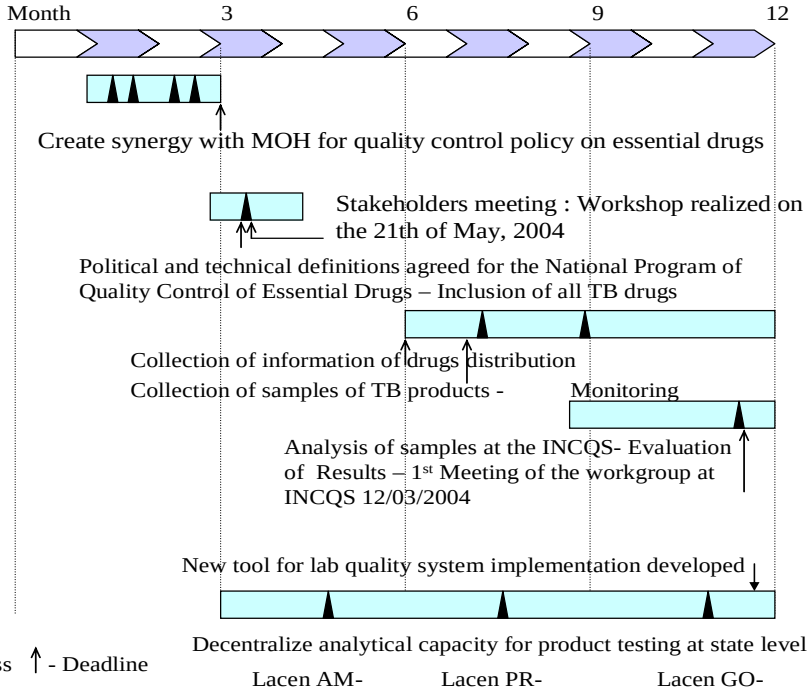
Overall Strategy



Testing quality of TB drugs
Strategy and achievements - FY03/FY04

1.Testing quality of TB drugs

- Create synergy with MOH for quality control policy on essential drugs
- Organize a stakeholders meeting with NTP, Anvisa, Pharmacy Department, INCQS (National Ref Lab), Lab Network, State Sanitary Surveillance
  - Regulation context for national program
  - Analytical capacity
  - Sampling procedures
  - Matrix of responsibilities
- Establish a working group carrying out activities and results monitoring
- **2. Decentralize Testing quality of TB drugs to state level**
- Decentralize analytical capacity for product testing in 11 states
- Develop new management and technical tools for laboratory (MOST* for Labs) : identify problems in quality systems and needed activities to move to ISO

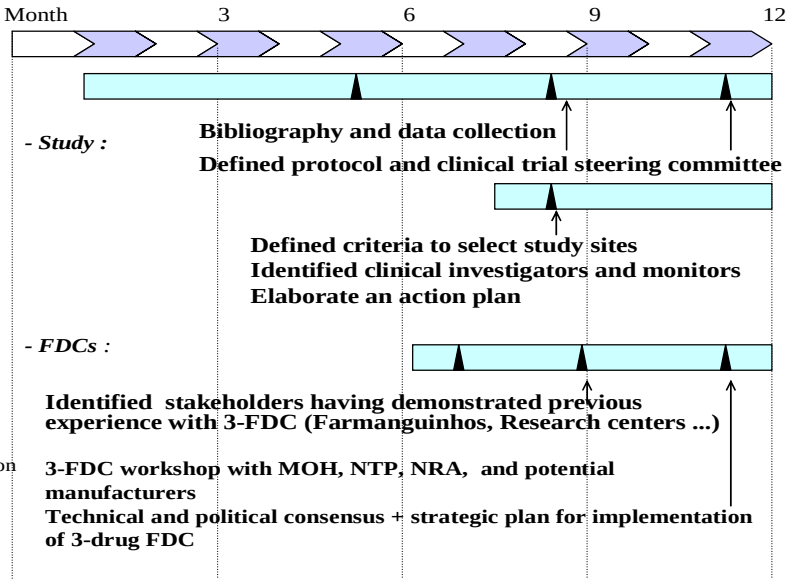


▲ - Meeting ▭ - Process ↑ - Deadline

Improving patient and prescriber compliance
Strategies and achievements -FY03/FY04

Strategies:

- Conduct studies to change regimen :
- Test 3SZEEt/9EEt versus 2S5ZELVF/4S2ZELVF/6ELVF
- Change to 3-FDC product RHZ



Outcomes

- First time industry, MOH programs, research institutions and NRA have met to harmonize issues in product formulation
- New 3-FDC =>85000 cases annually
-Reduces the number of tablets from 5-9 depending on patient weight to 3-4
-Replacement of capsules with tablet formulations

▲ - Meeting ▭ - Process ↑ - Deadline

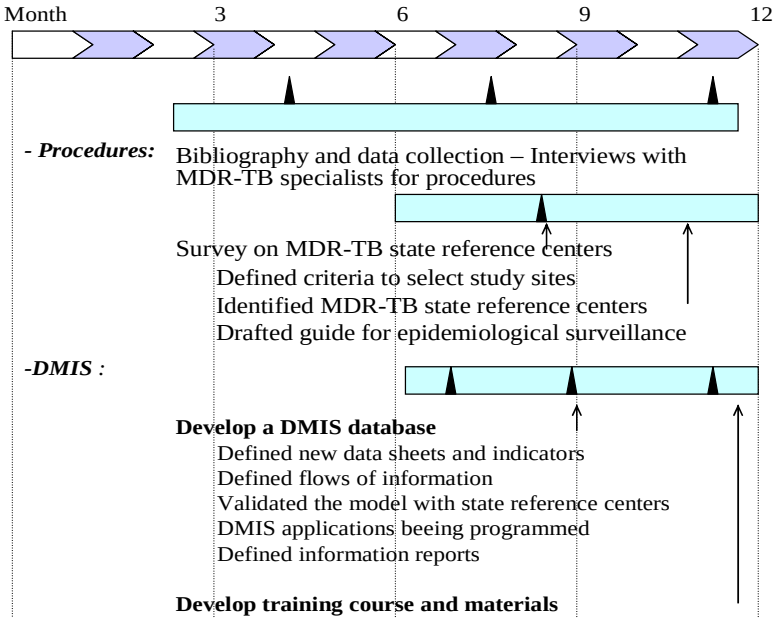
Decentralizing MDR-TB to states
Strategies and achievements - FY03/FY04

Strategies:

- Organize roundtable on how to decentralize to states
- Develop and validate procedures for states to follow
  - Modify diagnostic and treatment forms
  - Define indicators and control reports
  - Develop monitoring forms and define information flow
  - Harmonize with National Epidemiological Surveillance System (SINAN)
- Develop DMIS database
- Realize training workshops and conduct evaluation

Outcomes

Revised and edited manual of procedures for epidemiological surveillance of MDR-TB
Surveyed potential MDR-TB state reference centers
Identified MDR-TB state reference centers
Defined data sheets and DMIS information flow
Validated a decentralized model



- Meeting - Process - Deadline

Annex 4

Activity needs for FY05 (October 2005)

Streams of activities		FY05 OCT 1	OCT 2	OCT 3	JAN 1	JAN 2	JAN 3	APR 1	APR 2	APR 3	JUL 1	JUL 2	JUL 3	FY06 OCT 1	OCT 2	OCT 3
1. Decentralizing MDR-TB																
1.1 Apply the model to penal system	N															
1.2 Strengthen the State Reference Centers	N															
1.3 Evaluate efectiveness of the new DMIS	N															
2. Implementing FDC strategy for DOTS expansion																
2.1 3-FDC for new cases	C															
2.2 4-FDC for retreatment cases	C															
2.3 Promoting bio-availibility studies	N															
2.4 Develop materials for FDC introduction	N															
3. Developing strategy for treating resistant cases																
3.1 Obtain stakeholders consensus for regimen change	C															
3.2 Implement findings from regimen change	C															
3.3 Develop materials for regimen change	N															
4. Strengthening quality systems of the lab network																
4.1 Provide TA to certify new Lab at CRPHF	N															
4.2 Provide TA to certify Lacens for product quality assurance	C															

N New related activity
C Add-on activity